PERGAMON

European Journal of Cancer 38 (2002) 387–391

European Journal of Cancer

www.ejconline.com

Retreatment with dose-dense weekly cisplatin after previous cisplatin chemotherapy is not complicated by significant neuro-toxicity

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Received 12 March 2001; received in revised form 20 August 2001; accepted 19 October 2001

Abstract

Cisplatin induces a cumulative dose-dependent axonal sensory neuropathy. With a cumulative dose over 600 mg/m^2, a significant percentage of patients will develop a moderate or severe neuropathy. We retreated patients with progressive or recurrent ovarian cancer after previous platinum-containing chemotherapy with weekly 50–70 mg/m^2 cisplatin for six cycles. This group was prospectively followed for the development of neuropathy. Patients received six weekly cycles of either 50 or 70 mg/m^2 cisplatin, combined with oral etoposide. Responding patients continued treatment with daily oral etoposide for nine months. Neurological toxicity was assessed with a sensory sum score, the sensory neuropathy common toxicity criteria (CTC) and quantitated sensory analysis of the vibration perception threshold (VPT). Neurological assessment was scheduled at baseline, after three cycles, at the end of cisplatin chemotherapy and at 3 monthly intervals until 1 year after the discontinuation of chemotherapy. The first evaluation carried out in the interval of 1–4 months after the end of weekly cisplatin therapy was taken as the principle evaluation for neurotoxicity because during this time interval the nadir of cisplatin neurotoxicity is to be expected. Of 89 patients evaluated for neurological toxicity, 80 patients were fully evaluable. Forty-nine had received prior cisplatin (median cumulative dosage 450 mg/m^2); the others had received prior treatment with carboplatin. Cisplatin pretreated patients had slightly higher neuropathy scores at the start of weekly cisplatin. Almost all cisplatin pretreated patients received six cycles of cisplatin, 29 at 50 mg/m^2 and 20 at 70 mg/m^2 per cycle. Despite treatment up to an overall cumulative dose of 750–900 mg/m^2 cisplatin, only 1 patient discontinued treatment due to neurotoxicity. One other patient developed a grade 3 neuropathy during follow-up. Only a marginal increase of neuropathic signs and symptoms were observed in all the other patients. In multiple regression analysis, the increase in VPT or the sensory sum score was not related to prior treatment (cisplatin or carboplatin). Patients with mild signs of neuropathy after prior treatment with cisplatin to a cumulative dose level of 400–450 mg/m^2 can be retreated with weekly cisplatin to a cumulative dose of 420 mg/m^2 (overall cumulative dose up to 800–900 mg/m^2) with only a minimal risk of significant neurotoxicity.

Keywords: Cisplatin; Carboplatin; Salvage treatment; Ovarian cancer; Neurotoxicity; Neuropathy; Retreatment

1. Introduction

With the use of hypertonic saline, 5HT3 antagonists and dexamethasone to prevent nephrotoxicity and nausea/vomiting, peripheral neurotoxicity has become a major dose-limiting toxicity of cisplatin. Cisplatin causes a cumulative dose-dependent axonal sensory neuropathy which mostly affects the thick myelinated nerve fibres. Early symptoms of cisplatin-induced neuropathy are paresthesias, in more severe cases objective signs may vary from sensory deficits to a disabling sensory ataxia. There is a typical delayed time course of cisplatin-induced neuropathy, which often reaches its maximum 1–4 months after the last cycle of cisplatin chemotherapy [1,2]. The incidence of neuropathy rises steeply after a cumulative dose over 420 mg/m^2. After administration of 600 mg/m^2, neuropathy is frequent, and in up to 10% of patients disabling [1,3,4].

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0959-8049/02/$ - see front matter
PII: S0959-8049(01)00381-1

Platinum-containing chemotherapy (either cisplatin or carboplatin) is the cornerstone of medical treatment of ovarian cancer. Even patients relapsing after first-line platinum chemotherapy may respond to second-line chemotherapy with platinum [5,6]. Retreatment with cisplatin will result in a high cumulative dosage of cisplatin, and serious neurotoxicity must be anticipated. The few studies on retreatment with cisplatin paid only little attention to this possible side-effect. In our hospital, patients with relapsing or progressive ovarian cancer after first- (or second)-line platinum chemotherapy were treated with weekly cisplatin to an overall cumulative cisplatin dose of 750–900 mg/m^2. This report describes the neurological follow-up of 80 patients that were retreated with weekly cisplatin after previous platinum-based chemotherapy. 49 of those 80 patients had been treated previously with cisplatin, and 31 with carboplatin. Although this is not a randomised study, this allows the comparison between two similar patient groups differing mainly with respect to the previous type of platinum chemotherapy.

2. Patients and methods

All patients were treated as part of a treatment protocol for recurrent ovarian cancer. Eligible for this study were patients with histologically-verified recurrent ovarian cancer after prior treatment with platinum-containing chemotherapy, with World Health Organization (WHO) performance status 0–2, white blood cell (WBC) $>3\times10^9$, platelet count $>100\times10^9$/l, serum creatinine $\leqslant$120 μmol/l and Common Toxicity Criteria (CTC) sensory neuropathy score $\leqslant$2. Patients went off study if the creatinine clearance fell below 50 ml/min, if a CTC grade 3 neurotoxicity developed or if haematological recovery was insufficient. As part of the follow-up assessment of neurological toxicity was done during the treatment and 1 year afterwards (see below). This study protocol was approved by the ethical board of our hospital; all patients had to give informed consent. Patients were considered evaluable for neurological toxicity if they had neurological follow-up after a minimum of three cycles of weekly cisplatin. Treatment consisted of weekly cisplatin at a dose of 50 or 70 mg/m^2 on days 1, 8, 15 and 29, 36, 43, administered in hypertonic saline. Initially, patients were only included if they had a platinum-free interval of more than 1 year and they were treated with 50 mg/m^2 weekly cisplatin. Once this treatment appeared effective and showed little toxicity the study was extended to patients with a platinum-free interval of less than 1 year with the cisplatin dosage increased to 70 mg/m^2 weekly. Cisplatin was combined with oral etoposide 50 mg daily on days 1–15 and days 29–43. In cases of response or stable disease, treatment was continued with oral etoposide monotherapy at a dose of 50 mg/m^2 on days 1–21 every 4 weeks for a maximum of nine cycles.

2.1. Assessment of neuropathy

In order to reduce the burden of repeated neurological examinations, neuropathy was assessed with an easy to administer, short neurological assessment as described before [7–9]. This programme assesses peripheral neuropathy by a questionnaire for neurological symptoms, a standardised neurological examination and measurement of the Vibration Perception Threshold (VPT) as previously reported [1,2]. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon reflexes of the legs were each scored as normal (0) or abnormal (1). Sensory loss was defined as an abnormal test on either position sense, vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. Distal muscle strength in the lower extremities was tested. A sum score for each of these signs and symptoms was calculated which is expressed as the percentage of positive items. The severity of neuropathy was scored according to the National Cancer Institute (NCI) CTC for sensory neuropathy (Table 1). At each visit, the VPT was measured, which is a validated and easy method to monitor cisplatin-induced neuropathy [2,10]. VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic AB, Stockholm, Sweden) and recorded in micrometres (μm) of skin displacement. The Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The method of limits was used, which was repeated three times. Out of these observations the mean VPT was calculated [11]. Calculations on the VPT were carried out using the logVPT.

Neuropathy was assessed before the start of treatment, on day 28, on day 55 (the end of weekly cisplatin treatment) and thereafter every 3 months. In order to take post-treatment deterioration into account, the analysis of neurotoxicity was done on the first neuro-

Table 1
Severity of paresthesias and 'Common Toxicity Criteria' of the National Cancer Institute

CTC-Neurosensory
0 = no symptoms or signs
1 = mild paresthesias, loss of deep tendon reflexes
2 = moderate paresthesias, objective sensory loss
3 = severe paresthesias, sensory loss interfering with function

pathy assessment in the interval between days 30 and 120 after the last cisplatin administration.

3. Results

89 patients were evaluated at least once for neurological toxicity during their treatment with weekly cisplatin. 9 were not evaluable for neurotoxicity: 3 patients were lost to neurological follow-up, and 6 patients discontinued treatment for non-neurological toxicity-related causes: other toxicity (4), death (1) or refusal (1). Review of the medical records of these 9 patients did not reveal any clinical evidence of neurotoxicity.

Table 2 shows pretreatment characteristics of these patients. 31 had received prior treatment with carboplatin only, whereas 49 patients were pretreated with cisplatin. 11 of the cisplatin pretreated patients had also been treated with carboplatin at an earlier stage of their disease. In 4 patients (3 carboplatin) no baseline assessment was available. At baseline, signs and symptoms of a mild or moderate polyneuropathy were more frequent in the cisplatin pretreated group, which was reflected in the higher sensory sum scores, CTC scores and VPT scores.

In the cisplatin pretreated group, all patients except 4 received at least six cycles of weekly cisplatin, in 29 patients at a dose of 50 mg/m^2 per cycle and in 20 patients at a dose of 70 mg/m^2 per cycle (Table 3). In the carboplatin pretreated group, all but 5 patients received six or more cycles, and all but 4 received 70 mg/m^2. 9 patients received less than six cycles: 4 because of toxicity (in one because of neurotoxicity), 3 for unclear reasons, 1 for progressive disease, and 1 patient refused further cycles.

Table 4 shows the results of the overall neurological evaluations with weekly cisplatin. The increase in sensory sum score, CTC score and VPT (calculated as log VPT post-treatment−log VPT pre-treatment) was more pronounced in the carboplatin pretreated group. This was related to the lower pretreatment VPT and to the larger number of patients who received 70 mg/m^2 cisplatin in the carboplatin pretreated group. If the subgroups of patients treated with 70 mg/m^2 are compared, no statistical significant differences were found between patients pretreated with carboplatin ($n=25$) and those pretreated with cisplatin ($n=19$). With multiple regression analysis, the differences in post-treatment VPT were related to the pretreatment VPT, to the dose per cycle (50 mg versus 70 mg/m^2 cisplatin) and to the age of the patient. It was not related to the presence or absence of prior cisplatin treatment, nor to the time interval between the first and the second series of cisplatin treatment.

One patient discontinued treatment because of neurotoxicity. She had a CTC grade 2 neuropathy at the start of treatment, with an increased VPT. After four cycles of 70 mg/m^2, she developed difficulty in walking (CTC grade 3) and the VPT had increased further. Because of this, treatment was discontinued. 2 other prior cisplatin treated patients had a grade 3 CTC sensory neuropathy during follow-up, which was already present in 1 of them before salvage treatment with weekly cisplatin and did not change during treatment.

Table 2
Patient characteristics before the start of weekly cisplatin

	Carboplatin only pretreated	Cisplatin pretreated
Number of patients	31	49
carboplatin pretreated	31	11
Mean age (range) (years)	56 (32–75)	57 (26–78)
Cumulative dosage previous CPPD (mg/m^2) median (range)	–	450 (150–900)
Cumulative dosage previous carboplatin (mg/m^2) median (range)	2100 (1400–5250)	2100 (1050–2800)
Interval between prior treatment and weekly cisplatin		
<4 months	7	6
4–12 months	14	13
>12 months	10	30
CTC sensory score before the start of weekly cisplatin		
0 (none)	27	25
1 (mild)	0	17
2 (moderate)	1	5
3 (severe)	0	1
ND	3	1
Sensory sum score (0–100%)		
Mean; SD (range)	7; 13 (0–63)	29; 23 (0–100)
Pre-VPT		
Mean; S.D. (range)	0.8; 0.6 (0.2-2.8)	2.8; 5.9 (0.4-38.1)

S.D., standard deviation; CDDP, cisplatin; VPT, Vibration Perception Threshold; CTC, common toxicity criteria; ND, not determined.

4. Discussion

Our results demonstrate that platinum pretreated patients can be safely retreated with weekly cisplatin without significant neurotoxicity, despite an overall cumulative dosage of 750–900 mg/m^2 cisplatin. Treatment had to be discontinued in only 1 patient because of neurotoxicity, another patient developed a grade 3 CTC sensory neuropathy during follow-up. In the other patients, all measures for neurotoxicity showed only modest and clinically non-significant increases. Although at first glance it may seem that patients previously treated with cisplatin had less increase in VPT and sensory sum score than those pretreated with carboplatin, this difference is mainly related to the differences in the dosing schedule of weekly cisplatin: more carboplatin pretreated patients received 70 mg/m^2 per cycle. If only the patients treated with 70 mg/m^2 are compared, no differences in outcome of the post–pre log VPT and post–pre sensory sum score were observed. Linear regression analysis confirmed that the dose per cycle (50 mg versus 70 mg), the pretreatment VPT and the cumulative dose of weekly cisplatin were related to the post-treatment VPT and sensory sum score. No relationship was found with the type of platinum pretreatment (cisplatin versus carboplatin).

The overall cumulative dosage range reached in this study far exceeds the 500–600 mg/m^2 which, as a rule, results in a significant neurotoxicity if given as first-line chemotherapy [1,3]. With cumulative dose levels of 300–350 mg/m^2, only a few patients will develop a (usually mild) neuropathy. After treatment with 350–420 mg/m^2, up to 50% of patients may develop some signs and symptoms of neuropathy [1,12,13]. The incidence of neuropathy increases when dosages over 420 mg/m^2 are administered. After the administration of 600 mg/m^2, given in a relatively short time-span, almost all patients will develop some degree of neuropathy, 30–40% of patients will have a grade 2 neuropathy, while 10% will have a severe and disabling neuropathy [1,3,4].

Several studies have demonstrated a relationship between cisplatin toxicity and the dose schedule. Dividing the total cisplatin dose over several days is associated with less ototoxicity, gastrointestinal toxicity and nephrotoxicity [14,15]. A schedule with administration of cisplatin on days 1 and 8 was reported to be less toxic than the same total dose given over 5 days [16,17]. Cisplatin 100 mg/m^2 weekly for two triplets of 3 weeks separated by 5 weeks resulted in more ototoxicity than 100 mg/m^2 cisplatin every 3 weeks for six cycles [18]. Remarkably, in this randomised trial the neurotoxicity appeared less in the patients treated with weekly cisplatin. In a previous study, we concluded that cisplatin neuropathy is mainly determined by the cumulative dosage and not by the dose intensity [1,8]. In contrast, two other studies reported increased neurotoxicity after higher dose intensities of cisplatin [13,19].

Our present study suggests that the dose intensity is indeed the most important factor if the overall cumulative dose level is reached in two separate series of chemotherapy. Further support of the importance of the dose intensity can be derived from a series of patients treated up to a median cumulative cisplatin dosage of 560 mg/m^2 (range 210–760 mg/m^2) over a 1-year period, in which almost no neurotoxicity was observed [20]. Still, six of our prior cisplatin treated patients received weekly cisplatin for progressive disease within 4 months of the first-line cisplatin chemotherapy, without significant neurotoxicity. In these cases, retreatment started within the nadir of cisplatin neurotoxicity. Whether the weekly administration of cisplatin itself or the dissolution of cisplatin in hypertonic saline may have a beneficial effect on the occurrence of cisplatin neuropathy remains unanswered.

Low neurotoxicity of a potential neurotoxic treatment despite a high cumulative dosage has also been observed

Table 3
Cisplatin dose and number of cycles during weekly cisplatin treatment

	Pretreated with carboplatin only	Cisplatin pretreated
Dosage cisplatin per week		
50 mg/m^2	4	29
70 mg/m^2	27	20
Number of cycles weekly cisplatin		
3	1	0
4	0	2
5	4	2
6	25	38
9	1	7

Table 4
Post-treatment evaluations: CTC sensory neuropathy score, change in CTC sensory score compared with the baseline score (+ implies increase), Vibration Perception Threshold and the Sensory Sum Score

	Pretreated with carboplatin only	Cisplatin pretreated
CTC sensory score		
0	6	15
1	20	24
2	5	7
3	0	3
Change in CTC sensory score		
−1	0	2
+0	7	32
+1	18	11
+2	3	3
NE	3	1
VPT post-treatment		
Mean; S.D.	3.0; 1.7	4.1; 5.9
Sensory sum score (0–100%)		
Mean; S.D.	32; 1.7	37; 22

S.D., standard deviation; VPT, Vibration Perception Threshold; CTC, Common Toxicity Criteria; NE, not evaluable.

in patients treated with re-irradiation of the spinal cord and the brain for metastatic disease [21,22]. The overall cumulative dosage of radiation therapy delivered to neural structures in these studies is likely to produce severe neurotoxicity if given as a single series of radiation therapy, but no significant delayed neurotoxicity was observed. This demonstrates that cumulative dose-dependent detrimental effects of neurotoxic treatments do not need to be cumulative if the treatment is given in two series with an interval in between. Most likely, some repair mechanisms will be present.

In conclusion, retreatment with six cycles of weekly 50–70 mg/m^2 cisplatin after prior cisplatin chemotherapy to a cumulative dosage of 450 mg/m^2 can safely be administered without excessive neurotoxicity. Even the presence of mild signs and symptoms after prior cisplatin neuropathy (e.g. CTC grade 1-2 sensory neuropathy) is not a contra-indication for retreatment with weekly cisplatin.

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